**About AM-111**

AM-111 contains the cell-permeable JNK (c-Jun N-terminal Kinase) inhibitor peptide D-JNKI-1 formulated in a biocompatible and fully biodegradable gel. AM-111 blocks cell death (apoptosis) and attenuates inflammation following acute inner ear injury.

AM-111 is being developed for the treatment of acute sensorineural hearing loss (ASNHL): hearing loss from acoustic trauma, surgery trauma and sudden deafness (idiopathic sudden sensorineural hearing loss, ISSNHL). AM-111 is administered by intratympanic injection.

AM-111 received orphan drug designation from both the FDA and EMA.

In a Phase 2 clinical trial, AM-111 was well tolerated and showed a clinically relevant and statistically significant improvement in hearing and tinnitus (see below).

**Phase 3 Clinical Trials**

Auris Medical will conduct two pivotal clinical trials with AM-111 in the treatment of ISSNHL: HEALOS (Europe/Asia, initiated in Q4/2015) and ASSENT (USA, start Q2/2016). In both trials a single dose of AM-111 0.4 mg/mL or 0.8 mg/mL will be compared to placebo in patients suffering from acute severe to profound hearing loss within 72 hours from ISSNHL onset. Oral corticosteroids may be taken as reserve therapy or background therapy.

Mean hearing improvement at the three worst affected contiguous test frequencies (pure tone average, PTA) by Day 28 will be the primary efficacy endpoint. Further endpoints include the frequency of complete hearing recovery and of complete tinnitus remission and improvement in speech discrimination. Patients will be followed for 12 weeks.

In addition, Auris Medical is preparing a Phase 2 trial with AM-111 in the treatment of surgery-induced hearing loss called REACH (USA; start Q3/2016). AM-111 will be administered intraoperatively in patients with residual hearing who are undergoing cochlear implant surgery and who are at risk of losing residual hearing.

**Principal Phase 2 Results**

**Efficacy:** Patients with severe to profound hearing loss (those with PTA thresholds ≥ 60 dB) who were treated with AM-111 0.4 mg/mL showed an absolute improvement of hearing loss to Day 7 (primary endpoint) of 29.9 dB vs. 17.9 dB for the placebo group (p = 0.017). Outcomes were also significant for the co-primary endpoints relative hearing improvement and complete hearing recovery; in addition, speech discrimination at Day 7 improved by 27.4 vs. 9.1 percentage points (p = 0.019). Improvement in hearing threshold was clinically meaningful (> 10 dB better than placebo) already at Day 3. It con-tinued to do so up to the last follow-up visit at Day 90. The superior hearing recovery in the AM-111 0.4 mg/mL group vs. placebo was supported by more frequent complete tinnitus remission.

Improvement in the AM-111 2.0 mg/mL group was not significantly different from that observed in the lower dose group, although overall it was lower. Sensitivity analysis showed for both active treatment groups that the therapeutic effect did not depend on early treatment: in patients who were treated more than 24 hours after ASNHL onset, it actually was larger as the rate of spontaneous recovery decreased.

**Safety:** AM-111 was well tolerated and had no negative impact on hearing, balance or tinnitus. Adverse events were mostly local and procedure-related, as expected. Following i.t. injection, there were transient procedure-related effects such as ear discomfort or pain, incision site complications or middle ear infection in less than 5 % of patients.